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| EXAMINER | |
|---|---|
| WOLLENBERGER, LOUIS V | |

| ART UNIT | PAPER NUMBER |
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| 1635 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/800,362 | PARDRIDGE ET AL. | |
| | Examiner | Art Unit | |
| | Louis V. Wollenberger | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17,33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/23/07 has been entered.

### *Status of Application/Amendment/Claims*

Applicant's response filed 4/23/07 to the Final Action of 12/14/06 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/14/06 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 4/23/07, claims 1-17, 33, and 34 are pending and under examination. The amendment adds new claims 33 and 34.

***Election/Restrictions***

Applicants' arguments (Remarks, pp. 18 and 19) have been previously addressed in an earlier Action, mailed 12/14/06.

***Claim Rejections - 35 USC § 103—maintained***

Claims 1, 2, and 7–17 remain rejected and new claims 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (2002) *J. Gene Med.* 4:183-194, Shi et al. (2001) *PNAS* 98:12754–12759, and Paddison et al. (2002) *PNAS* 99:1443–1448.

The complete rejection is set forth in the Office Action mailed 3/8/2006.

Applicants' amendments to the claims, filed 4/23/07, add no structural or material limitations to the claimed nanocontainer. The newly introduced "wherein" clause, added to claim 1 merely recites an intended use. The "wherein" clause does not define the claimed invention other than by describing a capacity that the invention should have in a cell in vivo. Similarly, new claim 33 recites intended effects only and adds no additional structure to the invention recited in claim 1. New Claim 34 also recites intended effects---" wherein expression of the short hairpin RNA in the mammalian cell in the mammal inhibits expression of an endogenous gene of the cell"; however, the effect inferentially indicates that the shRNA recited in claim 1 is complementary to an endogenous gene.

With regard to claim 34, Zhang et al. taught receptor mediated delivery of a plasmid that expresses an antisense nucleotide sequence that is complementary to nucleotides 2317-3006 of the human EGFR mRNA, and Paddison et al. taught the inhibition of gene expression using

shRNAs that are expressed from plasmid constructs in mammalian cells. Paddison et al. teach structural requirements for plasmids that express shRNAs in mammalian cells and that short hairpin RNAs can induce sequence specific gene silencing in mammalian cells by endogenous expression of shRNAs in cells (pg. 949, col. 2).

Applicants are reminded that the claims are drawn to a product, not a method. In its broadest embodiment (claim 1), the product comprises four (4) components: 1) a liposome, 2) a gene encoding an shRNA, 3) a plurality of receptor targeting agents, and 4) a plurality of conjugation agents, connecting the targeting agents to the exterior surface of the liposome. Therefore, the body of the claim defines a structurally complete invention. The preamble and "wherein" clauses in the claim merely state a purpose or intended use for the invention and are given no patentable weight (MPEP 2111.02).

***Response to Arguments***

Applicant's arguments filed 4/23/07 have been fully considered but they are not persuasive.

The instantly claimed product is anticipated or rendered unpatentable by one or more references that teach and/or suggest the structurally complete product for use in any process, including in vitro, in vivo, ex vivo, or in any other assay of any kind.

Thus, the claimed invention is not limited to an *in vivo* embodiment of any kind. The claimed invention may have utility in vivo and may be intended for use in vivo, but the structurally complete invention as set forth in the claims may be properly rejected as unpatentable over prior art that taught or suggested the claimed combination of elements for use

in vitro, ex vivo, or in vivo or any other purpose which does not render the prior art device unsuitable for its intended purpose. The combination of prior art references cited herein taught methods for making and using receptor-targeted liposomes within the scope of the invention for research and therapeutic use in vitro, ex vivo, and in vivo. Thus, for example, it is not necessary for the Examiner to show that the device or product suggested by the combination of prior art references would have pharmacological effects, as Applicants appear to argue at page 14. Moreover, "intravenous administration" is not a required step, as the claim is not drawn to a method.

Therefore, Applicants' arguments (pp. 7-20) traversing the rejection on the basis that the combination of references do not provide a reasonable expectation of success *in vivo* are off point, do not address the claimed invention, and are not germane to the rejection.

Applicants acknowledge at page 8 that the combination of prior art references at least suggest the use in vitro. This is sufficient to reject the claimed invention. Moreover, the Examiner maintains that the cited prior art also enables use in vivo, until such evidence is provided persuasively showing otherwise.

Thus, while Applicants argue lack of reasonable expectation of success in vivo, they provide no evidence to substantiate this claim. For example, Applicants argue Tuschl et al. would not teach the skilled artisan how to implement RNAi in vivo, but provide no evidence for this assertion. Furthermore, the rejection does not stand on Tuschl et al. alone but on the combination of references. Further, the claims do not require delivery to cells in vivo, as the claims are not drawn to a method. Furthermore, so long as the combination of references would enable one of skill to make and use a structure within the scope of the invention to express a

single molecule of shRNA in any cell in any environment, the rejection is proper. Additionally, Applicant is reminded that absolute success or predictability is not required (MPEP 2143.02).

Applicants cite a presentation made by an Office employee with regard to in vivo RNAi (page 18), noting there is a low expectation of success for in vivo RNAi applications. The Examiner notes in passing that the instant claims have not been rejected for lack of enablement.

Inasmuch as the prior art teaches and/or suggests the structurally complete invention, and the disclosed prior art combination would have the capacity to express even a single (1) shRNA in a cell in vitro or in vivo, the claimed invention is disclosed for purposes of 35 USC 103.

Applicants also argue lack of motivation to combine the prior art references. The Examiner disagrees. As explained at length in an earlier Action (12/14/06), and as set forth in the original rejection (3/8/06), there is more than ample evidence in the prior art suggesting the use of receptor-targeted liposomes to deliver plasmid DNA encoding any nucleic acid, particularly shRNA, for both research and therapeutic purposes in cells in vitro, ex vivo, and in vivo. It is the Examiner's position that antisense and RNAi arts are analogous, that one of skill in the RNAi arts facing problems similar to those faced by antisense practictioners would look to the antisense arts for solutions and guidance, and that selecting proven delivery methods used by those in the antisense arts for use in RNAi applications would be obvious. The prior art shows delivery of antisense-encoding plasmid DNA for gene expression inhibition. It would have been routine for one of skill to engineer the plasmid DNA for expression of any nucleic acid, including shRNA, which the prior art suggests for use in gene expression inhibition.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Claim Rejections - 35 USC § 103—maintained***

Claims 3–6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (2002) *J. Gene Med.* 4:183-194, Shi et al. (2001) *PNAS* 98:12754–12759, and Paddison et al. (2002) *PNAS* 99:1443–1448 as applied to claims 1, 2, 7–17, 33, and 34 above, and further in view of Bennet et al. (U.S. Patent 5,914,269), Tuschl et al. (US 2004/0259247), Bass (2001) *Nature* 411:428-9; and Vickers et al. (2003) *J. Biol. Chem.* 278: 7108–7118.

The complete rejection is set forth in the Action mailed 12/14/2006.

***Response to Arguments***

Applicant's arguments filed 4/23/07 have been fully considered but they are not persuasive.

Applicants argue the combination of references fail to teach, suggest, or enable one of skill to make and use the claimed invention to inhibit gene expression in vivo.

The arguments are substantially identical to those raised in the rejection under 35 USC 103 above, and are not persuasive for the reasons given above. Intended in vivo use adds no patentable weight to the invention as claimed, other than requiring the mRNA be targeted to a gene.

The Examiner maintains that no contradictions exist in the prior art literature cited herein with regard to the art-recognized interchangeability and/or functional equivalency of antisense and RNAi agents, as alleged by Applicants. The claimed nanocontainers are clearly shown in the prior art to be capable of delivering plasmid DNA. The prior art taught shRNA-expressing

plasmids and shows that shRNAs provide similar rates of degradation to siRNAs. The prior art taught that target sites accessible to antisense agents are likely to be accessible to siRNA agents. No evidence has been provided that the shRNA-encoding plasmid DNAs would be incompatible with the receptor targeted liposomes, nor has any support been provided for statements arguing lack of success or motivation to make and use such liposomes with shRNA-encoding plasmids.

Therefore, the instant claims remain rejected for the reasons of record.

***Conclusion***

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LW
Art Unit 1635
June 13, 2007

/Sean McGarry/
Primary Examiner
AU 1635